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UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

ALKERMES, INC. and ALKERMES PHARMA IRELAND LIMITED, Plaintiffs, v. TEVA PHARMACEUTICALS USA, INC., Defendant.	Civil Action No. 20-12470 (MCA)(MAH) (Filed Electronically)

ALKERMES'S RESPONSIVE POST-TRIAL BRIEF

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TABLE OF ABBREVIATIONS

Parties	
Alkermes or Plaintiffs	Alkermes, Inc. and Alkermes Pharma Ireland Limited
Teva or Defendant	Teva Pharmaceuticals USA, Inc.
Patent-in-Suit	
'499 Patent	U.S. Patent No. 7,919,499, titled "Naltrexone Long Acting Formulations and Methods of Use," which issued on April 5, 2011, from Application No. 11/083,167 (PTX-1) (DTX-1)
'499 Patent Prosecution History	Patent Prosecution History of U.S. Patent No. 7,919,499 (DTX-002)
Asserted Claims	Claims 1, 2, 5, 10, and 13 of the '499 patent
Ehrich Declaration	Declaration Under 37 C.F.R. 1.132 of the inventor, Dr. Elliot Ehrich, filed March 17, 2005 (PTX-52) (PTX-179)
Patent-in-suit	The '499 Patent
References	
1995 SBIR Grant	1995 SBIR Grant (PTX-9)
Alim	Alim et al., *Tolerability Study of a Depot Form of Naltrexone Substance Abusers*, 153 NAT'L INST. ON DRUG ABUSE MONOGRAPH 253 (1995) (PTX-190) (DTX-124)
ALK21-003 Protocol	Protocol for Alkermes ALK21-003 Phase 3 Clinical Trial finalized on December 4, 2001 (PTX-235)
Chiang 1984	Chiang et al., *Kinetics of a Naltrexone Sustained-Release Preparation*, 36 CLINICAL PHARMACOLOGY AND THERAPEUTICS 704 (1984) (PTX-187) (DTX-131)
Chiang 1985	Chiang et al., *Clinical Evaluation of a Naltrexone Sustained-Release Preparation*, 16 DRUG AND ALCOHOL DEPENDENCE 1 (1985) (PTX-188)
Comer	Sandra D. Comer, et al., *Depot Naltrexone: Long-Lasting Antagonism of the Effects of Heroin in Humans*, 159 PSYCHOPHARMACOLOGY 351, 351-360 (2002) (PTX-18) (DTX-009)
Heishman	Heishman et al., *Safety and Pharmacokinetics of a New Formulation of Depot Naltrexone*, 141 NAT'L INST. ON DRUG ABUSE MONOGRAPH SERIES 82 (1994) (PTX-23) (DTX-216)
Kranzler	Henry R. Kranzler, *Sustained-Release Naltrexone for Alcoholism Treatment: A Preliminary Study*, 22(5) ALCOHOLISM: CLINICAL AND EXPERIMENTAL RESEARCH 1074, 1074-1079 (1998) (PTX-25) (DTX-217)
Leavitt	Stewart B. Leavitt, *Evidence for the Efficacy of Naltrexone in the Treatment of Alcohol Dependence (Alcoholism)*, ADDICTION TREATMENT FORUM 1, 1-10 (2002) (PTX-27) (DTX-133)
Nuwayser	E. Nuwayser, U.S. Patent No. 7,157,102, titled "Multi-Layered Microcapsules and Method of Preparing Same," (DTX-215)

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Olsen	Olsen et al., *A Review of Parenteral Sustained-Release Naltrexone Systems*, 28 NAT'L INST. ON DRUG ABUSE MONOGRAPH SERIES 187, 187-193 (1981) (PTX-36) (DTX-140)
Remington	*Remington's Pharmaceutical Sciences*, Anthony R. DiSanto, Bioavailability and Bioequivalency Testing, Ch. 76 (1990) (PTX-76)
Sullivan	Sullivan et al., *A Randomized Trial Comparing Extended-Release Injectable Suspension and Oral Naltrexone, Both Combined With Behavioral Therapy, for the Treatment of Opioid Use Disorder*, 176 AM. J. PSYCHIATRY 129, 129-137 (2019) (PTX-40)
Tice	Tice et al., U.S. Patent No. 6,306,425, titled "Injectable Naltrexone Microsphere Compositions and Their Use in Reducing Consumption of Heroin and Alcohol" (PTX-44) (PTX-191) (DTX-137)
Verebey	Verebey et al., *Narcotic Antagonists: Naltrexone Pharmacochemistry and Sustained-Release Preparations*, NALTREXONE: RESEARCH MONOGRAPH 28, 147-158 (1980) (DTX-213)
Vivitrol® Label	Vivitrol® Label, revised Oct. 2010 (DTX-004), revised May 2020 (PTX-48), revised Mar. 2021 (DTX-166)
Pleadings	
COL	Plaintiffs' Post-trial Proposed Conclusions of Law
PFOF	Plaintiffs' Post-trial Proposed Findings of Fact
R-COL	Plaintiffs' Responsive Post-trial Proposed Conclusions of Law
R-PFOF	Plaintiffs' Responsive Post-trial Proposed Findings of Fact
TPFF	Teva's Post-trial Proposed Findings of Fact
Alkermes Br.	Alkermes's Opening Post-trial Brief
Teva Br.	Teva's Opening Post-trial Brief
Miscellaneous	
AUC	Area under the curve
FDA	U.S. Food and Drug Administration
NIDA	National Institute on Drug Abuse
PK	Pharmacokinetic
PLGA	Polylactide-co-glycolide
POSA	Person of ordinary skill in the art
PTAB	U.S. Patent Trial and Appeal Board

I. Introduction

In its opening arguments, and through its expert witnesses (Dr. Westreich and Dr. Yaman) in its case-in-chief, Teva asserted that its obviousness defense was that a POSA (in April 2004) would have combined Comer, Nuwayser, and Leavitt to arrive at the claimed invention. (D.I. 198 at 1-2 (Teva "will only be relying on its Comer + Nuwayser + Leavitt obviousness combination"); *accord* Westreich 89:2-5; Yaman 260:5-7; Teva's Counsel 248:1-4, 248:13-17.) *In its post-trial submissions,* Teva has done an about-face, trying to use purported "impeachment" testimony of the fact-witness inventor to fabricate another theory of obviousness based on Alkermes's own work that is not supported by the evidence of record, the testimony of the witnesses, or the law. The question for alleged obviousness is not what the inventor knew or thought — that is impermissible hindsight — but, instead, what a hypothetical, ordinarily skilled artisan, in April 2004, would have thought from Teva's prior art. Teva failed to prove by clear and convincing evidence that such a POSA would have arrived at each of the Asserted Claims without hindsight.

Turning to its theory based on the prior art, Teva cannot have a POSA ignore the Comer paper's express teaching that the higher 384 mg naltrexone dose resulted in "significantly elevated" cravings for heroin (without increased withdrawal) through attorney-argument claiming that it was just "one metric." In particular, the trial *evidence* showed the significance of this finding. The Comer paper itself brought the finding forth in the "Discussion" section. And, Teva's own expert, Dr. Westreich, admitted that a POSA, looking for a treatment of dependence that improved on oral naltrexone, would not wish to increase cravings for heroin. Teva also ignores its obligation to show a non-hindsight reasonable expectation of success from the prior art, since the Comer paper was not demonstrating a successful treatment of any person's heroin dependence, and certainly not in a manner that would improve compliance over oral naltrexone.

Teva also failed to prove obviousness of the claimed comparative AUC limitation. Because Dr. Westreich admitted that nothing in the prior art taught "the pursuit of a depot form of naltrexone that has a three times greater plasma AUC than oral naltrexone" (*see, e.g.*, Westreich 207:16-19), Teva — not Alkermes — had to prove "that the claimed AUC ratio is inherent to the administration of the 384 mg dose of the long-acting naltrexone-PLGA Depotrex formulation" (Teva Br. at 27-28). Teva's assertion that the claimed AUC value "is an inherent property of administering a long-acting formulation of 310–480 mg of naltrexone within any PLGA polymer" (Teva Br., 3), is again more attorney-argument, belied by, *inter alia*, Dr. Yaman's own testimony that the same dose of naltrexone in different long-acting PLGA formulations can have different AUC properties.

The evidence Teva advanced at trial though Dr. Yaman's so-called cross-study comparisons was exposed by Dr. Peck as "the single most-common error" in interpreting data, citing a leading treatise, which Dr. Yaman never addressed. Not surprisingly, the Ehrich Declaration and the Tice reference discussed in that declaration, which must be considered in deciding Teva's defenses, never used such cross-study comparisons. Instead, the Ehrich Declaration and the Tice reference rely on the standard comparative PK study. Put simply, Teva's mixing and matching of unrelated studies is unreliable science, which cannot satisfy Teva's heavy burden for proving inherency by clear and convincing evidence.

Teva's half-hearted "alternative" theory (lack of written description) also falls far short of meeting Teva's burden. Teva incorrectly asserts, with no testimonial support, that a POSA could not achieve the claimed AUC limitation without step-by-step instructions set forth in the patent claims and specification. But the trial evidence showed that the specification not only provides a working example of the invention, but also uses that as a basis for other express teachings about

the desired characteristics of the invention, including details about PLGA ratios, examples of PLGA polymer systems for use in the embodiments of the claims, and the ultimate goal of a three-times comparative AUC property used in a method of treatment not previously taught in the prior art.

Ultimately, what Teva's Opening Brief did not address speaks directly to why Teva did not prove its claims of patent invalidity by clear and convincing evidence:

- Dr. Yaman never disputed that the standard and accepted way for conducting a comparative AUC analysis presented in the Asserted Claims is a single comparative pharmacokinetic study in healthy patients, and he provided no evidence of variability using this form of study;
- Under *Markman* and *Phillips* claim construction principles, the '499 Patent claims require a treatment using a single injection of a long-acting naltrexone formulation containing PLGA and the specified amount of naltrexone in the injection (310-480mg for Claim 1 and 380 mg for Claim 5), and which achieves the claimed comparative AUC;
- Kranzler recommended "***reducing*** the total dose of naltrexone ***in each injection***" from 206 mg in the Depotrex formulation because of painful indurations, and BioTek never created a Depotrex formulation using a single injection of naltrexone containing more than 206 mg thereafter, including in the Comer paper;
- There was no clear and convincing evidence that giving 384 mg of naltrexone using the BioTek Depotrex formulation (whether in two injections as in Comer or, as Teva posits using impermissible hindsight, as new single injection) would ***necessarily*** (*i.e.*, as the law requires) result in a three times greater AUC than oral naltrexone;
- There was no clear and convincing evidence that each dependent claim (*e.g.*, claim 10 specific to treating alcohol dependence with a single injection of the formulation of Claim 1) would have been obvious;
- Nexus is presumed between the objective indicia and the '499 Patent and those objective indicia must be considered as further reflecting Teva's failure of proof; and
- Dr. Yaman admitted that a POSA, following the '499 Patent, would have known how to make a long-acting formulation according to the '499 Patent to achieve the claimed invention.

II. Teva Failed to Prove Indefiniteness by Clear and Convincing Evidence

A. Teva Is Wrong That "It Is Impossible To Determine Whether a Formulation Will Actually Meet [The Claimed] AUC Result Or Not"

Teva does not and cannot dispute that it determined precisely what it now argues is "impossible to determine": The AUC of its long-acting naltrexone formulation meets the claimed AUC by being about three times higher than the AUC of the oral 50 mg daily naltrexone formulation and Teva stipulated to infringement of the Asserted Claims. (*See, e.g.*, PTX-144.0016; Lahoz (PTX-268) at 13:23-14:01; 65:22-66:11, 66:18-68:01 (discussing PTX-144.0016); D.I. 58.)

In asserting that "neither the claims nor the specification of the patent provides any guidance regarding what individuals to evaluate, or, if an oral AUC value from the literature should be used, which one" (Teva Br. at 12, 14-15; *see* Yaman 302:19-25), Teva relies on a flawed legal premise, *i.e.*, that definiteness is judged on the express wording of the patent claims and specification, without the existing knowledge of a skilled artisan reading those words or the prosecution history. (COL ¶¶ 310-312.) Patent claims do not have to expressly recite a measurement technique if a POSA would have sufficient guidance from their knowledge as a skilled artisan. *Presidio Components, Inc. v. Am. Tech. Ceramics Corp.*, 875 F.3d 1369, 1376 (Fed. Cir. 2017) ("[A] claim is not indefinite if a person of skill in the art would know how to utilize a standard measurement method . . . to make the necessary measurement," and "[a] patent need not explicitly include information that is already well known in the art."). And the ***skilled artisan*** versed in pharmacokinetics (for whom the patent is written) has not just the patent claims

and specification as a source of guidance, but also the ***patent prosecution history (i.e., the Ehrich Declaration)***. (Alkermes Br. at 36-38; COL § X.F.)

Under the proper legal standard, Teva fails to meet its heavy burden of proof because the evidence at trial established that a POSA would:

- understand that the patent claim language is referring to a ***comparison*** of the AUC of the long-acting formulation and the AUC of the 50 mg/day oral naltrexone (PFOF ¶ 247);
- understand that the patent specification makes multiple references to this comparative 3.3 times AUC value, as determined from clinical studies using Vivitrol® (*see* Little 920:14-18; *see also* '499 Patent at .0007 (1:33-39, 2:23-29, 2:34-36));
- know how to determine the comparative AUC value using "a human pharmacokinetic trial" (Yaman 393:3-9; *see also* PFOF ¶ 247);
- understand that such human pharmacokinetic trials for making AUC comparisons are performed in a single study of healthy subjects (PFOF ¶¶ 183, 248-251);[1] and
- confirm that understanding with a review of the Ehrich Declaration in the patent prosecution history, which showed a single pharmacokinetic human study that produced the comparative 3.3 times AUC value determination.

At trial, Teva placed its burden of proving indefiniteness by clear and convincing evidence on the shoulders of its expert formulator, Dr. Yaman. Dr. Yaman admitted, however, that he is not an expert in pharmacokinetics, clinical trials, or the design of a human pharmacokinetic ("PK") study, and that he would rely upon a pharmacokineticist to design the protocol for such a study. (*See* Yaman 393:15-394:5; PFOF ¶¶ 43, 254.) The only pharmacokineticist who testified at trial was Alkermes's expert, Dr. Peck, a medical doctor with decades of experience with PK evaluations and designing clinical trials. (PFOF §§ II.A.3, II.B.2.) Dr. Peck's expert opinion regarding how a POSA would understand the claims was not only informed by his expertise in the area, but

[1] As Dr. Peck testified at length, the single comparative PK study was "standard," not only in 2004, but since he started in the field in 1972. (PFOF § VIII.A; R-PFOF ¶¶ 31-33, 43; Peck 459:23-460:25; 464:1-25.) Dr. Yaman did not provide any testimony to rebut this.

supported by the prosecution history and the scientific evidence demonstrating a POSA's knowledge. (PFOF §§ II.A.3, VIII.A; COL § X.F; Alkermes Br. at 36-38.)

Teva also attempts to leverage Dr. Yaman's discussion of the "first pass" effect of oral naltrexone and the unremarkable fact that the bioavailability of oral naltrexone — like other oral drugs — can have some variation in specific individuals, to argue that "there are many potential AUC values for oral naltrexone" for a POSA to choose from other studies in the prior art. (Teva Br. at 11-12 (citing Yaman 291:16-20).) As Dr. Peck testified, however, the first-pass effect is and has long been a well-known phenomenon that is "not unique to naltrexone" and "applies to many, many drugs." (Peck 473:7-18; 473:23-474:2; *see* PFOF ¶¶ 254-255; *see also* Yaman 288:10-16.) Yet, this does not prevent scientists from using PK studies of oral drugs to make valid scientific conclusions and relying on them for drug approvals, as do generics like Teva all the time. (PFOF ¶ 254 n.34; Peck 459:23-460:12, 475:2-8.) Dr. Peck testified, without rebuttal, that the first-pass effect in specific individuals would not be problematic in a single PK study because, *inter alia*, a POSA "deals with the variability by using good clinical trial designs and good data analysis methods." (Peck 474:7-15, 475:6-8; *see* PFOF ¶¶ 254-55 & n.34, 255.)[2] And, as Dr. Yaman admitted on cross-examination, a generic manufacturer submitting an application for an oral tablet routinely measures bioequivalence to the branded drug through a PK study using comparative AUC values, and does so even though the individuals taking the branded drug and

[2] Teva asserts that "the oral AUC values for the two different cohorts of subjects tested by Dr. Ehrich . . . varied significantly from each other" (Teva Br. at 12), but comparing two different cohorts to each other is just that — two different groups and thus an improper cross-study comparison. Teva's witnesses provided no evidence of such variability, however, when comparing a long-acting formulation and the oral formulation from a cohort in a single PK study, as is scientifically sound. (PFOF ¶ 255.) In fact, the comparative AUC for each cohort in Dr. Ehrich's declaration showed that Vivitrol had the same 3.3 times greater AUC compared to the oral naltrexone tested in that same cohort. (R-PFOF ¶ 36.)

the generic drug in the bioequivalence study may all have variable AUC due to the first-pass effect. (*See* Yaman 394:6-25; *see also* R-PFOF ¶ 35.) Dr. Yaman's discussion of the first-pass effect was therefore a "distraction." (Peck 474:7-8; PFOF ¶ 254.)

Teva also continues to rely (Teva Br. at 11-14) on AUC ratios Dr. Yaman created from comparing unrelated studies to one another, *i.e.*, invalid cross-study comparisons, even though the preeminent treatise on pharmaceutical sciences cautions that cross-study comparisons are "dangerous and can lead to false conclusions," which Dr. Peck explained is "a common pitfall, that is a way ***not*** to do things." (PFOF ¶¶ 183, 255; Peck 457:6-459:20, 476:15-24; PTX-76.0008-0010.)[3] Before Dr. Peck had testified, however, Teva led Dr. Yaman squarely into that "pitfall." Because the undisputed evidence shows that a POSA would ***not*** use a cross-study comparison like Dr. Yaman did, Dr. Yaman's arguments of variability, entirely premised on scientifically unsound cross-study comparisons lacks probative value and fails to satisfy Teva's heavy burden of proving invalidity by clear and convincing evidence. (*See* COL § X.F.)

Although Teva presented no evidence of such calculations at trial, Teva argues that the comparative AUC determination should be made in a sick patient in need of naltrexone (Teva Br. at 14-15), once again ignoring the guidance to a POSA provided by the Ehrich Declaration confirming that the comparative AUC study is performed in healthy individuals (PFOF ¶¶ 142, 250-53; R-PFOF ¶¶ 59-61). The trial testimony showed that a POSA would have known this anyway because the comparative AUC value is a property of the design of the formulation, and that formulation is what is used in the method of treatment. (PFOF ¶ 251.) The use of healthy

[3] Teva misleads when it argues that Alkermes did not "assert that Dr. Yaman's calculations demonstrating how the AUC ratios would change were incorrect." (Teva Br. at 14.) Dr. Peck spent considerable time doing just that. (PFOF § VIII.A.)

patients is a standard, scientifically sound way to limit variability in a comparative PK study. (PFOF ¶¶ 250-51.)

Dr. Yaman admitted that a POSA would have understood that "Vivitrol achieves a three-times-greater AUC" based on "the data in Dr. Ehrich's declaration," which was "a pharmacokinetic study that Dr. Ehrich conducted ***in healthy subjects***." (Yaman 396:21-24, 397:8-16.) Further, Dr. Westreich agreed that "Alkermes included in the label to the FDA a reference to the comparative AUC versus oral naltrexone." (Westreich 226:17-227:10; *see also* Vivitrol® Label (2010) at .0009.) And even Teva itself agreed that the comparative AUC calculation is "confirmed by Dr. Ehrich's data showing that giving [Vivitrol® to healthy subjects] resulted in an AUC three times that of the oral dose." (Teva Br. at 22.)

Finally, although not a point addressed by Teva's experts, Teva now seeks to sow confusion by relying on its cross-examination of Dr. Peck to argue that Dr. Ehrich's study "does not comply" with a POSA's understanding of how a comparative PK study would be conducted because not all 28 subjects in the study who received oral naltrexone were then given Vivitrol®. (*See* Teva Br. at 15 (citing TPFF ¶108).) Teva ignores, however, that ***all*** the individuals receiving the long-acting formulation had also been given oral naltrexone, and in this way there was control for variability. (PFOF ¶¶ 142, 250, 252; PFOF ¶¶ 142, 250, 252.) Unsupported attorney argument, contradicted by the standard method for conducting these types of studies, does not satisfy Teva's burden. (PFOF ¶ 252 n.31; R-COL ¶¶ 485-491.) Dr. Peck testified (without contradiction) that, because this is a within-study and not a cross-study comparison, (1) there would be good reason to use as many subjects as possible from the same arm of the trial and (2) the best estimate for comparative AUC would come from using all individuals in the groups receiving those drugs in the single study. (Peck 498:8-16; R-PFOF ¶¶ 66-70.) Furthermore, Tice — the only prior art

reference cited by Teva that compared AUCs of oral and long-acting naltrexone (targeting comparable AUC values between the two) — is consistent with Dr. Ehrich's methodology: a single PK study of a single injection of long-acting naltrexone compared to oral naltrexone administered in the same study. (PFOF § IV.C.11, ¶ 255 n.36.) Neither Teva nor Dr. Yaman identified any variability because of Dr. Ehrich's methodology or an alternative way to conduct a proper AUC comparison based on prior art evidence available to a POSA in 2004.[4]

B. Teva Failed to Prove Indefiniteness of the Comparative AUC Time Interval

Teva's second line of attack ignores that the invention is a method of treatment and not merely a formulation or an AUC value. (*Compare* Teva Br. at 16 (framing issue based on the formulation) *with* Westreich 226:3-8; Little 792:20-25 (recognizing the invention is a treatment method).) And, because Teva admitted infringement, Teva's hypotheticals about "infringement" of unknown formulations divorced from reality and which ignore the way those theoretical formulations would be used in a treatment method are simply irrelevant. It goes without saying that many, many patent cases (but not this one) involve genuine issues of infringement, and patents

[4] With no showing by Teva that equally alternative, valid methods of performing comparative AUC studies exist other than a single PK study, which would create outcome-determinative variability, Teva's cases are inapposite. *See HZNP Meds. LLC v. Actavis Lab'ys UT, Inc*., 940 F.3d 680, 697-98 (Fed. Cir. 2019) (two valid methods proven for evaluating "better drying time," and no guidance to a POSA on which to use); *Dow Chem. Co. v. Nova Chems. Corp*., 803 F.3d 620, 634 (Fed. Cir. 2015) (four known methods proven for calculating the slope, but the evidence did not "provide any guidance as to which method should be used"); *see also* R-COL ¶¶ 484-491. In *Forest Lab'ys, Inc. v. Teva Pharms. USA, Inc*., Teva argued that a POSA would conduct a single PK study — just as Dr. Peck opined here — but because the patentee had declined to agree with Teva, the patentee waived the argument that the release profiles should be measured in the same human study. 716 F. App'x 987, 994-95 (Fed. Cir. 2017).

are, of course, not indefinite even in cases where a judge or jury has significant infringement issues to weigh and decide.

In the present case, as the patent itself discloses, when using a long-acting naltrexone formulation in the inventive method of treatment, the treatment designer specifies the time interval between administrations. (PFOF ¶ 257.) "As such, the formulation can be administered weekly, with a one-week release formulation, biweekly with a two-week release formulation, or monthly with a four-week release formulation." ('499 Patent at .0008 (4:51-55); PFOF ¶¶ 259-61.) Vivitrol® is as an example of a four-week release formulation. ('499 Patent at .0008 (4:51-55); PFOF ¶¶ 259-61.) The evidence at trial established that a method of treatment will have a defined time period, and the use of the long-acting formulation will be matched to that period.[5] (PFOF § VIII.B.) Dr. Yaman agreed that "when designing a long-acting pharmaceutical product containing a bioequivalence polymer, you will typically have an intended time period for release of the drug after administration." (Yaman 395:1-6.) The time period for calculating the comparative AUC value matches this treatment period. (PFOF ¶¶ 256-58; Little 840:17-21, 841:8-21.) This straightforward application of the claim matches the way in which comparative AUC values were calculated in all the evidence at trial using such comparisons, including Vivitrol®, Teva's ANDA product, the Ehrich Declaration, and the Tice patent. (PFOF § VIII.B; R-PFOF ¶¶ 39, 45, 72; *see* Peck 483:24-484:8; *see also* Little 841:13-842:4; Yaman 395:1-6, 396:15-20.)

Teva argues, with no evidentiary support, that "subjective intent of the formulator" could impact the infringement determination (Teva Br. at 16), ignoring the actual claimed treatment

[5] The invention of the Asserted Claims provides a method of treating patients in need of naltrexone with a long-acting formulation. (*See* Little 791:23-792:25; Ehrich 709:1-21; *see also* '499 Patent at .0007 (1:31-40), .0017.) Such a long-acting naltrexone formulation, among other things, avoids the need for patients to take a daily oral pill as done in the prior art. (PFOF § IV.B.)

method. (PFOF ¶ 261; R-PFOF ¶¶ 75-78; R-COL ¶¶ 492-495; Little 853:23-862:10.) The time interval is an ***objective*** feature of the treatment method, and is plugged into an ***objective*** mathematical formula for calculating the comparative AUC. (PFOF § VIII.B; Little 854:24-856:15, 859:22-860:5.) The claims here are nothing like patents that include subjective phrases like "aesthetically pleasing" or "unobtrusive manner" that turn on "matters of taste or preference." *See Sonix Tech. Co. v. Publications Int'l, Ltd.*, 844 F.3d 1370, 1378 (Fed. Cir. 2017) (distinguishing *Interval Licensing LLC v. AOL, Inc.*, 766 F.3d 1364 (Fed. Cir. 2014), and *Datamize, LLC v. Plumtree Software, Inc.*, 417 F.3d 1342 (Fed. Cir. 2005)). Nor do the claims here depend upon a particular user's "subjective notions" to buy a product, as in *Amazon.com, Inc. v. Barnesandnoble.com, Inc.*, 239 F.3d 1343, 1353 (Fed. Cir. 2001).

Finally, Teva's erroneous arguments do not apply to ***Claim 2***, which is presumed valid independent of the other claims. (COL ¶ 277.) In Claim 2, the treatment period is limited to "four weeks." ('499 Patent at .0017 (Claim 2).) There was no dispute at trial that a POSA, reading this claim and the Ehrich Declaration, would recognize that the four-week treatment period (*i.e.*, 28 days) matches the four-week period for calculating the AUC ratio. (PFOF ¶¶ 257, 259-60.) Dr. Yaman admitted that "Dr. Ehrich describes the intended use of Vivitrol in his declaration as a 28-day time period" and "calculated the AUC of Vivitrol over that 28-day time period." (Yaman 396:15-20.)

III. Teva Failed To Apply the Correct Construction of Claim 1 Requiring That Individuals Be Treated With a Single Injection of a Formulation Containing the Specified Naltrexone Dose That Achieves the Specified Comparative AUC Values

Even though it is legal error to consider patent validity without first using the rules of *Markman* and *Phillips* to interpret a claim properly, Teva does just that when it leaps into discussions of validity with the most conclusory and paltry references to claim interpretation. (*Compare* Alkermes Br. at 7-9; PFOF § III.D; COL ¶ 273 *with* Teva Br. at 26.)

Alkermes's Opening Brief contains a proper claim construction. (Alkermes Br. at 7-9.) As shown there, the claim language reflects a single injection, expressing the "step" of administering "a formulation" containing the specified amount of naltrexone. (PFOF ¶¶ 66-68, 74.) The other claims and the patent specification reinforce that the invention is a single injection. (PFOF ¶¶ 69-72, 74-75.) The Ehrich Declaration unequivocally represents that the invention "is" a "single injection." (PFOF ¶¶ 73, 76.) This is important because the method of treatment is not like some immediate-release product (like an EpiPen®) that goes quickly into the bloodstream. Instead, the injection is a long-acting PLGA polymer formulation that resides at the site of injection for an extended period as it degrades and releases the drug into surrounding capillaries and then into the general blood circulation. (*See* Little 788:18-790:7.) The single injection also allows alternating each month between buttocks, over the course of months of use of the drug. (Vivitrol® Label (2010) at .0001.) Alkermes's successful treatment with a single-injection formulation was proven to be a benefit in improving patient compliance. (PFOF ¶ 226; *see* Weiss 608:2-609:3; *see also* Sullivan at .0001.)

Against all this specific evidence, Teva makes a generic argument that the word "a" means "one or more" in open-ended claims containing the transitional phrase "comprising," citing a non-precedential case with dissimilar facts. (Teva Br. at 26 (citing *Rehco LLC v. Spin Master, Ltd.*, 759 F. App'x 944, 949 (Fed. Cir. 2019)); *see also* R-COL ¶¶ 511-513; R-PFOF ¶ 249.) Unlike *Rehco*, the word following "comprising" in the '499 Patent Claim 1 is a definite article ("the step") of administering "a formulation," making Teva's generalized rule inapplicable. (Alkermes Br., 8; PFOF § III.B, D; *see also Harari v. Lee*, 656 F.3d 1331, 1341 (Fed. Cir. 2011) (where claim refers to "a bit line" to activate a number of cells, "[t]he plain language of the claim clearly indicates that only a single bit line is used when accessing a number of cells").) Moreover, such a generalization

"does not apply when the specification or the prosecution history shows that the term was used in its singular sense." *Norian Corp. v. Stryker Corp.*, 432 F.3d 1356, 1359 (Fed. Cir. 2005); *Abtox, Inc. v. Exitron Corp.*, 122 F.3d 1019, 1023-27 (Fed. Cir. 1997) (construing the phrase "comprising . . . a metallic gas-confining chamber" to be a single such chamber based on the specification); *Elkay Mfg. Co. v. Ebco Mfg. Co.*, 192 F.3d 973, 977-79 (Fed. Cir. 1999) (construing the phrase "comprising . . . an upstanding feed tube" to be a single tube based on the prosecution history); *see also* COL ¶ 274; R-COL ¶¶ 511-513. The Federal Circuit has reversed claim constructions that fail to carefully consider the usage of language in the patent specification, claims, and prosecution history, in addition to arguments about ordinary meaning. *See, e.g.*, *AstraZeneca AB v. Mylan Pharms. Inc.*, 19 F.4th 1325, 1329, 1335 (Fed. Cir. 2021).

Teva's proposal does not even make sense. If "the step of parenterally administering ***a*** long acting formulation" were administering ***one or more*** formulations in multiple injections, each formulation injected would still need to have the specified amount of naltrexone (310-480 mg), and so each injection would add that amount of naltrexone (*e.g.*, two injections totaling 620-960 mg). The specification does not describe such large dosing in a single step, and Teva does not offer any prior art that involved such a method of treatment.

Teva also makes much of a confusing line of cross-examination of Dr. Little (Teva Br. at 26) about FDA instructions for the exigent circumstance where the Vivitrol® needle clogs and the user is instructed to continue the injection of the specified amount in the same injection area. (*See* Little 911:14-917:19; *see also* R-PFOF ¶¶ 264-267.) But that FDA label instruction is not evidence relevant to construing the patent under Federal Circuit precedent. (*See* Alkermes Br. at 33 n.20; R-COL ¶¶ 507-510.) Further, Teva's experts never discussed it or relied on it. (*See* PFOF ¶ 218 n.28; Alkermes Br. at 33 n.20; Little 911:14-917:19 (counsel presenting argument for the first time

during cross examination).) Teva ignores that the ordinary and intended use of Vivitrol® is a single injection of 380 mg of naltrexone without a clogged needle. (*See* R R-PFOF ¶¶ 264-267.) And that ordinary and intended use unquestionably embodies and infringes the '499 Patent claims. (D.I. 58; PFOF ¶¶ 218-221.)

Finally, Teva holds out the PTAB institution decision, which no witness testified about, to incorrectly argue that "the prosecution history confirms that the claimed administration may be performed in multiple injections." (Teva Br. at 26.) A cursory review of that decision, however, shows that the PTAB never engaged in claim construction for the Claim 1 step of administering "a long acting formulation" containing the specified amount of naltrexone. (R-PFOF ¶¶ 262-263, 388; R-COL ¶¶ 503, 516.) And, even if it had, the PTAB at that time applied legal standards for claim construction different than what district courts must apply. (*See* D.I. 207.)[6] Moreover, the PTAB was deciding only whether to begin an IPR proceeding — on a record that is not of record in this case and that included expert declarations different from those here, with the evidence viewed most favorably to the patent challenger. It has no probative weight and creates a danger of legal error and unfair prejudice.

IV. Teva Did Not Prove by Clear and Convincing Evidence That the Asserted Claims Would Have Been Obvious to a POSA Over Comer, Nuwayser, and Leavitt at the Time of the Invention

A. Teva's Post-Trial Attempt to Shift Its Obviousness Theory by Attacking the Inventor and Relying on Alkermes's Own Work Fails to Meet Teva's Burden

At trial, Teva and its experts presented an obviousness theory that a POSA would combine Comer, Nuwayser, and Leavitt, and arrive at the invention. (*See* D.I. 198; *accord* Westreich 89:2-

[6] Alkermes respectfully refers the Court to its bench memorandum submitted during trial that shows that the preliminary PTAB institution decision is not probative and should be given no weight. (*See* D.I. 207.)

5; Yaman 260:5-7; Teva's Counsel 248:1-4, 248:13-17.) Teva's post-trial brief is now a full turn away from this theory, placing central reliance on non-prior art Alkermes documents allegedly presented at a "San Juan" conference, and assaulting the honesty and integrity of the inventor, a fact-witness scientist who does not currently work for Alkermes and appeared at trial voluntarily to explain the thinking that led to his invention. That desperate tactic fails for the numerous legal and factual reasons discussed below. Indeed, Teva's arguments about this conference (1) cite cross-examination of a fact witness who was not at the conference, (2) refer to documents that were not entered into evidence (or included in the Final Pretrial Order), and (3) were never discussed or relied on by any of Teva's experts. Fundamentally, however, attacking Dr. Ehrich's explanation of his invention does not prove obviousness under any standard, let alone by clear and convincing evidence. *Millennium Pharms., Inc. v. Sandoz Inc.*, 862 F.3d 1356, 1367 (Fed. Cir. 2017) ("[An] inventor's own path itself never leads to a conclusion of obviousness; that is hindsight.").

First, Teva asserts that "the claimed AUC properties would have been entirely expected in view of . . . ***Alkermes's prior disclosure*** of the AUC data at the conference in San Juan in 2000." (Teva Br. at 27-28 (emphasis added).) The document this argument alludes to is not in evidence. The cross-examination testimony did not establish that the particular documents shown to the witness were in fact presented. And Teva failed to prove that, even if they had been, the presentation would legally constitute prior art or be combined by a POSA with unrelated BioTek Depotrex publications. (R-PFOF ¶¶ 185-190; R-COL ¶¶ 522-523.) The basis for Teva's argument is Dr. Ehrich's cross-examination testimony, purportedly for "impeachment," where he stated "[t]hat's my interpretation," in response to being asked whether a "poster" (not a slide deck or

abstract) was "presented with Alkermes's information at the San Juan meeting."[7] (Ehrich 775:7-10.) Teva knew of — but did not designate — testimony about these documents from Mr. Bartus, who Teva alleged was actually involved in the conference. (*See generally* DTX-237.) Mr. Bartus had testified at deposition that the "presentation" document (shown to Dr. Ehrich at trial) contained "draft slides" and he could not say that he presented slides containing AUC data at the San Juan conference. (*See* R-PFOF ¶¶ 185-190.) It is hardly credible that, if Alkermes had published its invention in the prior art, Teva would have spent its entire case-in-chief on Depotrex and BioTek, never raising this alleged presentation with its experts. In fact, Dr. Westreich admitted his opinions "did not identify ***any*** prior art reference that discusses the pursuit of a depot form of naltrexone that has a three times greater plasma AUC than oral naltrexone." (Westreich 207:16-19 (emphasis added).)

Further, for Teva to use documents or information allegedly presented at a San Juan conference for its obviousness argument, Teva needed to prove, by clear and convincing evidence, that these materials were accessible to the public and that a POSA would have thought to combine them with the unrelated BioTek publications. *See Cordis Corp. v. Boston Scientific Corp.*, 561 F.3d 1319, 1332-35 (2009). Teva did not even try to meet this burden. Again, Teva confronted Dr. Ehrich with these documents on cross-examination while failing to disclose that Mr. Bartus had testified that the San Juan conference was likely not public; it was in fact restrictive and

[7] Moreover, it is unclear what "Alkermes's information" is being discussed when Teva references a "poster" because at trial Teva only showed Dr. Ehrich an "abstract" and a "slide." (Ehrich 745:13-25, 749:20-750:8.) A poster is a different form of document, more like those displayed at a science fair. Also, Teva referred on cross to testing amounts of naltrexone (*i.e.*, 150 mg, 300 mg, 600 mg, and 900 mg) that were never actually tested. (*Compare* PTX-235 at .0016 *with* ALK21-003 Protocol at .0016 (describing the doses tested in ALK21-001 as 141 mg, 269 mg, 530 mg, and 784 mg).) Teva twists an internal draft document, which the author, Mr. Bartus, was unable to confirm was a final version. (*See* R-PFOF ¶¶ 185-190, 341.)

required confidentiality, further indicating Teva's gamesmanship. (R-PFOF ¶¶ 185-190; R-COL ¶¶ 522-523.) And none of Teva's experts even asserted, let alone demonstrated, that a POSA would have combined Alkermes's information with unrelated publications by BioTek. Accordingly, Teva invites legal error by asking the Court to find invalidity based on information that was not relied on by its experts, is not in evidence, and was not proven to constitute prior art. *See Barry v. Medtronic, Inc.*, 914 F.3d 1310, 1327 (Fed. Cir. 2019) (not prior art when the evidence supports an implied obligation of confidentiality that precludes public accessibility).

Teva's post-trial brief also conflicts with its representation to the Court (to avoid an evidentiary objection) that Teva was not relying on the San Juan conference for proving obviousness, but only for allegedly "impeaching [Dr. Ehrich's] testimony." (Teva's Counsel at 744:16-745:11.)

Second, grasping at straws, Teva uses this non-prior art to accuse Dr. Ehrich of committing fraud on the patent office. (*See* Teva Br. 9-10.) More than ten years ago, the Federal Circuit sought to stop infringers from making these kinds of fraud accusations as an end-run around their heavy burden of proving obviousness. In *Therasense, Inc. v. Becton, Dickinson & Co.*, 649 F.3d 1276, 1290 (Fed. Cir. 2011), the Federal Circuit warned that such accusations had become an "absolute plague" on the patent system, so the Court imposed heightened standards for proving such an accusation. *Id.* at 1289. On top of that, the Federal Circuit mandated that infringers who assert fraud on the patent office must plead those assertions with heightened specificity in its answer under Fed. R. Civ. P. 9(b). *See, e.g.*, *Ontario Inc. v. Best Deals Disc. Furniture LLC*, No. 22-03557, 2023 WL 3072756, at *2-3 (D.N.J. Apr. 25, 2023) (citing *Exergen Corp. v. Wal-Mart Stores, Inc.*, 575 F.3d 1312, 1326-27 (Fed. Cir. 2009)). Despite questioning Mr. Bartus about the "San Juan" presentation during his deposition, Teva never pleaded or pursued a fraud defense,

does not address the legal requirements for making these accusations in its brief or conclusions of law, and does not come close to meeting the standards for proving fraud. Teva cannot satisfy its heavy burden by taking shots at Dr. Ehrich, who is a respected clinician and former Chief Scientific Officer who voluntarily came to trial as a fact witness to tell the Court about his invention.

Putting all of that aside, what Teva says (Teva Br. 7-8) is incorrect and misstates the record. As Dr. Westreich ***admitted*** at trial, "the patent office examiner considered the Comer reference ***before allowing the '499 patent***." (Westreich 186:3-6 (emphasis added).)[8] The Comer paper is listed on the ***cover page*** of the '499 Patent as one of the "References Cited" (*see* Westreich 185:17-24; '499 Patent at .0002). Further, the Kranzler paper, another of Teva's cited "Depotrex" publications, is specifically discussed in the specification of the '499 Patent as an example of a prior art "long-acting injectable naltrexone formulation." (*See* '499 Patent at .0015 (17:53-62).) Teva has no support for its assertion (Teva Br. at 7-8) that Alkermes never informed the Patent Office about Depotrex or Depotrex prior art before the patent issued.

Third, Teva insinuates with absolutely no evidentiary proof that Alkermes copied the Comer paper to invent Vivitrol®.[9] (*See* Teva Br. at 7-8.) Besides being rank speculation, which cannot support an obviousness finding, the timelines do not match up. Teva cites an email from 1999, two years ***before*** the Comer paper published, that discusses basic formulations, not

[8] Even a cursory review of the file history shows that Alkermes specifically identified Comer (*see* '499 Patent Prosecution History at .0633, .0665) and the Examiner considered it when allowing the patent to issue (*see id*. at .0692). Alkermes also identified Leavitt, which is listed on the cover of the '499 Patent as a "Reference[] Cited" ('499 Patent at .0002), and the Examiner considered it during prosecution ('499 Patent Prosecution History at .0356, .0367, .0470).

[9] Teva's willingness to speak without support from both sides of its mouth to attack Alkermes and Dr. Ehrich illustrates its kitchen sink approach of baseless attacks to distract from a failure of proof: Teva asserts that Alkermes publicly disclosed the invention in San Juan in 2000, and also that Alkermes's invention occurred later, after supposedly copying the 2001 Comer paper. Neither assertion is right.

treatments or dosing of naltrexone. (*See* Ehrich 772:7-17; DTX-007 at .0001-2; Comer at .0007.) Likewise, Alkermes began its clinical trials for Vivitrol® more than a year ***before*** the Comer paper was published. (*See* ALK21-003 Protocol at .0002, .0015-16; Comer at .0007; *see also* Ehrich 761:23-762:15.) There is no evidence Alkermes employed the BioTek formulation, and instead the evidence shows that Alkermes focused on its own Medisorb® formulation technology. (*See, e.g.*, Ehrich 687:2-19; DTX007.0002.) In fact, in the cited email, Alkermes noted problems with the BioTek process such as producing large microcapsules and the potential for adverse reactions caused by the BioTek formulation. (DTX-007.0002.) Further, Teva did not show how a POSA could have relied on an internal email from Alkermes to combine with prior art. If Teva actually had a claim for theft of invention, Teva would have argued a defense of "derivation" under 35 U.S.C. § 102(f), instead of using innuendo in the guise of an obviousness argument. To be sure, in all the years since the '499 Patent issued, Vivitrol®'s clinical trials were published, and FDA approved the drug, BioTek never made such a claim.

Fourth, Teva's attempts to attack the credibility of Dr. Ehrich's invention story at trial (Teva Br. at 7-9) are irrelevant to the issues in this case. There is no requirement that an inventor describe his or her invention story in detail in the patent. *See, e.g.*, *Diamond Rubber Co. of N.Y. v. Consol. Rubber Tire Co.*, 220 U.S. 428, 435-36 (1911) ("It is certainly not necessary that [an inventor] understand or be able to state the scientific principles underlying his invention, and it is immaterial whether [the inventor] can stand a successful examination as to the speculative ideas involved."). Moreover, to the extent Teva is suggesting that other people besides Dr. Ehrich at Alkermes were also inventors (Teva Br. at 7-9), Alkermes could simply correct the listed inventors under 35 U.S.C. § 256 (*see* Westreich 89:2-5; Yaman 260:2-10; D.I. 198; *see also* Teva's Counsel

248:1-4, 248:13-17). For these reasons, Teva's unwarranted attacks on Dr. Ehrich and his invention story should be disregarded in analyzing whether Teva proved its obviousness defense.

B. Teva Failed to Prove, by Clear and Convincing Evidence, That Claims 1 and 5 Would Have Been Obvious Over Comer, Nuwayser, and Leavitt

1. A Cherry-Picked, Cross-Study Comparison is Unreliable to Show that the Comparative Naltrexone AUC Was Inherent to 384 mg of the BioTek Depotrex Formulation (in Either a Single or Double Injection)

Recognizing that nothing in the prior art taught "the pursuit of a depot form of naltrexone that has a three times greater plasma AUC than oral naltrexone" (*see, e.g.*, Westreich 207:16-19), Teva attempts to improperly shift the burden to Alkermes to disprove that "that the claimed AUC ratio is inherent to the administration of the 384 mg dose of the long-acting naltrexone-PLGA Depotrex formulation" (Teva Br. at 27-28; *see* COL ¶ 289). *See, e.g.*, *Endo Pharm. Solutions v. Custopharm Inc.*, 894 F.3d 1374, 1381 (Fed. Cir. 2018) (a party cannot rely on "probabilities or possibilities" to establish inherency, but must show that the limitation at issue is "necessarily" present in the prior-art combination). Teva presented no evidence that a hypothetical 384 mg Depotrex formulation given as a single injection would have resulted in about three or 3.3 times greater plasma AUC than oral naltrexone, as required respectively by Claims 1 and 5, including because no modified 384 mg Depotrex formulation for single injection was ever made or tested. (PFOF ¶¶ 173, 178.)

Even under Teva's erroneous construction of the claims that would allow for two injections totaling 384 mg to meet the claims, Teva failed to satisfy its burden. Teva relies on Dr. Yaman[10] to assert that the two injections in two buttocks of BioTek's 192 mg formulation resulted in the

[10] Dr. Yaman admitted to conducting ***cross-study comparisons*** between data reported in the Comer paper and data reported in "***unrelated studies***" with no similarity to the Comer study. (Yaman 400:7-10 (emphasis added); *see also* PFOF ¶¶ 181-186.)

claimed AUC ratio (Teva Br. at 22), but his only basis for that assertion was his improper and unreliable cross-study comparisons, which the undisputed evidence showed are not a scientifically valid or acceptable means of determining comparative AUC and, more importantly, cannot prove an inherent AUC of that formulation. (PFOF § VI.B.2; COL ¶ 289 R-PFOF 231-232.)

Teva is also wrong that Dr. Yaman "appl[ied] Dr. Ehrich's AUC methodology before the Patent Office." (Teva Br. at 22.) Dr. Ehrich's AUC methodology used ***a single PK study***, where both the oral naltrexone and long-acting naltrexone were tested in the same group of healthy subjects. (PFOF ¶ 142.) Teva highlights the flaws in Dr. Yaman's cross-study comparison when it cites him using that procedure to opine that "the exact same drug formulation can both produce the claimed ratio of about three ***or not*** produce that ratio, entirely depending on which [oral] AUC measurements are used." (Teva Br. at 12 (emphasis added); *see also* Yaman 301:22-25; PFOF ¶¶ 183-184.) Dr. Yaman's self-contradictory opinions do not show inherency. (COL § X.D; R-COL ¶¶ 542-544.)

Teva also cannot legitimize Dr. Yaman's cross-study comparison by asserting that he "assume[d] that the ***AUC of the oral naltrexone*** and ***the time-period for the AUC*** of the long-acting naltrexone ***are identical*** to the ones used in Dr. Ehrich's declaration." (Teva Br. at 19 n.3 (emphases added).) Not only is such mixing and matching unreliable science, but assuming particular AUC values while ignoring others cannot establish inherency. Further, this assumption is not even accurate because Dr. Yaman relied on oral AUC data from the Tice patent, as well as two different oral AUC results from Dr. Ehrich's declaration, and found at times a ratio of 2.6 instead of 3.3 times. (*See* Yaman 336:4-337:3; R-PFOF ¶¶ 145-148.) Dr. Yaman's selective use

of data from unrelated studies is not valid and also demonstrates hindsight bias.[11] (PFOF ¶¶ 182-185.)

Dr. Yaman admitted that the same dose of naltrexone in different long-acting PLGA formulations can have different AUC properties. (PFOF ¶ 180.) The Comer paper used one specific naltrexone formulation from BioTek. Teva did not prove by clear and convincing evidence that this particular BioTek formulation used in the Comer study achieved the claimed comparative AUC value.[12] To be sure, a POSA who has knowledge of the claimed invention, including use of PLGA, the doses, and the goal of achieving a comparative three-times AUC, can readily design a formulation with the claimed amount of naltrexone that achieves the comparative AUC value. (PFOF ¶¶ 180, 266-268.) But that does not logically imply that every different formulation with the given dose (and no knowledge of the AUC goal and thus no design work to achieve it) would necessarily result in the same AUC value.[13]

And even if Teva could show that the comparative AUC was "probable" or "possible" from the two injections of the BioTek formulation, Teva ***still fails to satisfy the legal standard for***

[11] Teva cannot rely on *Purdue Pharma Prods. L.P. v. Par Pharm., Inc.*, 377 F. App'x 978, 983 (Fed. Cir. 2010), because in *Purdue* a single prior art reference was proven to have disclosed the claimed PK values, which is not the case here.

[12] Teva's admission that "the specific choice of PLGA polymer could . . . affect the properties of the formulation, which would include its AUC," is fatal to its inherency argument. (Teva Br. at 39.) Teva makes that admission when it improperly conflates two different and unrelated legal issues — written description and nonobviousness. (*See* Alkermes Br. at 38-39.) Alkermes further responds to that defense in Section V below.

[13] The only evidence of a comparative AUC determination in the prior art was Tice's disclosure that a 300 mg naltrexone-PLA formulation achieves an AUC ***comparable*** to oral naltrexone, underscoring that the formulation containing naltrexone impacts the AUC. (*See* PFOF ¶¶ 180, 180 n.23.)

inherency, which requires proving, by clear and convincing evidence, that the comparative AUC limitation is ***necessarily*** present. (COL ¶ 289.)

Finally, Teva argues inherency is "further confirmed by Dr. Ehrich's data showing that giving [Vivitrol®] to patients also resulted in an AUC three times that of the oral dose" (Teva Br. at 22), but the evidence presented at trial demonstrated that the BioTek formulation and Alkermes's formulation were not the same (R-PFOF ¶¶ 175, 274). Further, despite Teva's unsupported assertions,[14] Vivitrol® was not a "prior art embodiment," so Teva cannot rely on *Hospira, Inc. v. Fresenius Kabi USA, LLC*, 946 F.3d 1322, 1329-30 (Fed. Cir. 2020) to say the inventor's work proves inherency.

2. Teva Failed to Prove That a POSA Would Have Been Motivated from the Prior Art to Treat Dependence by Administering a Single Long-Acting Injection of 310-480 mg of Naltrexone Without Hindsight, as Claim 1 Requires

The trial record showed significant concerns that a POSA would have had after reading the Comer paper's teaching that persons addicted to heroin who received the higher 384 mg naltrexone dose experienced "significantly elevated" cravings for heroin. (PFOF ¶ 158.) Teva cannot sidestep this finding from the Comer paper by calling it just "one metric." (Teva Br. at 31-32.) Neither the trial witnesses nor the Comer paper viewed the information that way. The Comer paper included these "dramatic" findings in the "Discussion" section, specifically ruling out that the increased cravings were due to withdrawal. (PFOF ¶ 117; *see also* Comer at .0014.) Dr. Westreich did not testify that a POSA would not have been impacted by this discussion.

[14] Teva again resorts to mischaracterizing its alleged impeachment attempt as actual evidence in this case, asserting that Alkermes disclosed the claimed AUC properties at "the conference in San Juan in 2000." (Teva Br. at 27-28.) As discussed above, Teva's cross-examination does not prove what this information actually was, that it constitutes prior art, or that a POSA would have combined this information with unrelated information from BioTek.

Instead, he admitted that a POSA, with the goal of treating dependence, would have wanted to ***minimize*** cravings, and having increased cravings would only further deter patient compliance. (PFOF ¶¶ 116-118, 158-164.) He also admitted that the 192 mg naltrexone dose performed better in this regard. (PFOF ¶¶ 116-117, 162-163.) Dr. Weiss explained that Comer's teaching of increased cravings would have dissuaded a POSA from using that higher dose for treating dependence. (PFOF ¶¶ 118, 164.)

Teva also cannot avoid Comer's teaching by claiming that "the prior art repeatedly noted that naltrexone treatments were generally well tolerated," because Teva is citing safety and efficacy established for ***50 mg/day oral naltrexone***. (Teva Br. at 33.)[15] For example, DTX-183, cited in TPFF ¶ 140, found that "[t]he most common adverse effects reported with the use of naltrexone at a dosage of 50 mg/day include nausea and vomiting. Naltrexone does not appear to be hepatotoxic ***in dosages recommended in the treatment of alcohol dependence, i.e. 50 mg/day***." (DTX-183.0001 (emphasis added); *see also* PFOF ¶¶ 90, 100, 124, 147, 165-170, 195.)[16] Departing from the established safety and efficacy that resulted from naltrexone exposure after 50 mg/day of oral naltrexone would directly conflict with Teva's asserted motivation for a POSA to develop a long-acting formulation in the first place. (*See* Alkermes Br. at Argument § I.B; PFOF § VI.A.) Moreover, as Dr. Westreich admitted, the prior art did not teach "the pursuit of a depot

[15] Teva cites TPFF ¶ 460, which mischaracterizes Dr. Weiss's publication dated 2004. (Teva Br. at 33.) Dr. Weiss's 2004 publication is not prior art, and Teva's misleading questions on cross-examination ignore that the article included reporting about Alkermes's discussions of its own non-prior art clinical trials. (Weiss 653:13-656:14 (explaining that the 2004 publication was "pointing out ongoing studies with Vivitrex and expressing some hope that it may hold promise for improved treatment outcomes"); R-PFOF ¶¶ 193, 325, 331; R-COL ¶ 522.)

[16] As Dr. Weiss explained, although Comer states that certain side effects were not observed, this was only in six subjects, who received a round of naltrexone injections and were also receiving increasing doses of ***heroin***. (PFOF ¶ 198.) As such, a POSA could not rule out side effects for a larger group from the nature of this small, preliminary study. (PFOF ¶ 198.)

form of naltrexone that has a three times greater plasma AUC than oral naltrexone." (Westreich 207:16-19.) Increasing a patient's exposure to naltrexone without any good reason would have required a POSA in April 2004 to depart from the established safety and efficacy of the standard naltrexone treatment at the time (50 mg/day oral naltrexone), which a POSA would have thought could exacerbate the known side effects associated with naltrexone itself, such as nausea, anxiety, or increased liver enzymes. (Alkermes Br. at 21-22; PFOF ¶¶ 165-170, 195; COL § X.D.)

Teva also applies improper hindsight when arguing that a POSA would arrive at a single injection containing 384 mg naltrexone. (PFOF § VI.B.1; COL § X.D.1.) Teva does not dispute Kranzler's recommendation for "***reducing*** the total dose of naltrexone ***in each injection***" from 206 mg because of painful indurations (hardening of the skin) that resulted from a single injection of that amount of naltrexone. (PFOF § IV.C.7, ¶ 174.) Teva's arguments that Comer failed to observe injection site reactions misses the point of Kranzler's conclusion because Comer ***divided*** the double dose of 384 mg into two injections of 192 mg each, given in two buttocks. (PFOF § IV.C.8.) Kranzler and Comer reflect the lack of clear and convincing evidence that a POSA in April 2004 would have dramatically ***increased*** the amount of naltrexone per injection beyond what Kranzler used, going all the way to 384 mg of naltrexone in a single injection to treat dependence. (*See* Little 882:3-20; 891:18-892:19; *see also* PFOF ¶ 176.) Teva invokes improper hindsight to assert that a POSA would have made this significant leap.

Teva's hindsight is reinforced by the fact that BioTek ***never*** made or tested a dose higher than 206 mg in a single injection after the Kranzler paper, including in the Nuwayser patent filed after the Comer paper. (PFOF ¶¶ 171-178.) Teva has not established a non-hindsight motivation in the prior art for a POSA to do what the Comer and Nuwayser publications actually did not do

— administer a single injection of a long-acting formulation containing 384 mg of naltrexone in a PLGA polymer.

Rather than address these prior art teachings that undermine Teva's alleged motivation to arrive at the claimed invention (Alkermes Br. at 19-24; PFOF § VI.B.1), Teva raises and attacks a strawman argument that a POSA had no desire for a long-acting treatment for dependence (an argument that neither Alkermes nor its witnesses presented). (Teva Br. at 32-33.) Teva also seeks to improperly flip the burden on Alkermes to prove that the teachings of the Comer and Kranzler publications regarding cravings and indurations taught away from the claimed invention (*id.*),[17] ignoring established Federal Circuit case law that, "even if [a reference] does not teach away," negative statements in the prior art are still "relevant to a finding regarding whether a skilled artisan would be motivated to combine." *See, e.g., Apple Inc. v. Samsung Elecs. Co.*, 839 F.3d 1034, 1051 n.15 (Fed. Cir. 2016) (en banc); *Rembrandt Wireless Techs., LP v. Samsung Elecs. Co.*, 853 F.3d 1370, 1379-80 (Fed. Cir. 2017); *see also* COL ¶ 288. Indeed, as is the case here, an inference of non-obviousness is especially strong where the prior art's teachings undermine the very reason being proffered as to why a person of ordinary skill would have combined the known elements. *See, e.g., Allergan, Inc. v. Sandoz Inc.*, 796 F.3d 1293, 1306 (Fed. Cir. 2015); *see also* COL ¶ 288.

[17] Teva's cited cases (Teva Br., 33) either do not address "teaching away or a lack of motivation to combine" (R-COL ¶¶ 553-556) or found the evidence of teaching away not relevant to the claims at issue (R-COL ¶¶ 558-559). Here, the claims are to a method of treatment of dependence using a long-acting formulation, which to a POSA thus implicates safety, efficacy, and tolerability. (PFOF ¶ 61, 197, 215-216; Westreich 178:7-11 ("a POSA in 2004 would have been looking for a long-acting naltrexone treatment that was ***safe and effective*** and would ***improve patient compliance*** compared to oral naltrexone") (emphases added).) Regardless, there is no dispute that Alkermes proved its invention of Vivitrol® was safe and effective, and improved patient compliance. (PFOF ¶ 226.)

3. Teva's Assertion That a POSA Would Have Been Motivated to Achieve Naltrexone Plasma Levels of "1-2 ng/mL" Has No Merit

Teva's post-trial obviousness theory is premised on the argument that a POSA would have been motivated to target "therapeutic plasma levels (>1-2 ng/mL)" for a month (Teva Br. at 19-20), but this "therapeutic level" was rejected by Teva's own witnesses and contradicted by Teva's primary reference, the Comer paper.

Teva misconstrues Dr. Yaman's testimony in an attempt to change his trial testimony *post hoc*. (*See, e.g.*, Teva Br. at 20 (citing TPFF ¶ 219).) Dr. Yaman did not testify that the targeted "therapeutic level" for naltrexone treatment was "1-2 ng/mL." (PFOF ¶ 155 n.15; R-PFOF ¶¶ 155-159.) Actually, he opined, albeit incorrectly, that ***2 ng/mL*** was the "***minimum*** plasma naltrexone level" a POSA would target. (Yaman 312:13-313:4, 419:1-5; *see also* Yaman 309:12-310:8.) He went further to argue that a POSA would ***not*** be motivated to target "some lower target like 1 [ng/mL]." (Yaman 312:17-313:4, 419:1-5.)[18] Teva is therefore arguing against its own witness.

Dr. Yaman attempted to apply his 2 ng/mL or greater target to the data provided in Comer paper (Yaman 352:16-353:25 (discussing DDX-3.70)), but the evidence at trial demonstrated why that opinion is deeply flawed,[19] and contradicted by the Comer paper itself. The Comer paper reported that "negligible" blood plasma levels of naltrexone (***around 0.3 ng/mL***) antagonized heroin's effects, which (1) corroborated recent studies that also found effective antagonism at negligible plasma naltrexone levels, and (2) negated the findings from earlier studies hypothesizing higher blood levels as a minimum target. (PFOF ¶¶ 114, 155 n.15; *see also* R-PFOF ¶¶ 155-159.)

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[18] Teva misleadingly cites Dr. Yaman reading Heishman and Alim referencing 1-2 ng/mL. (Teva Br. at 6 (citing TPFF ¶¶ 161, 164).) But after reading those portions from Heishman and Alim, Dr. Yaman then argued that a POSA "would target the 2 [ng/mL] target plasma level . . . ***or greater***." (Yaman 326:1-12; 349:3-5; *see also* Yaman 346:17-347:2.)

[19] According to Dr. Yaman's own figure, the Comer paper reported that the double dose of 384 mg dropped below 2 ng/mL long before day 29. (*See* Comer at .0011; *see also* DDX-3.70.)

Because Dr. Yaman admitted that he is not an expert in "how naltrexone works to treat alcohol or opioid dependence" or "what was known clinically about naltrexone," he said he would "look to target the plasma levels that a clinician [such as Dr. Westreich] told [him] to achieve for naltrexone." (Yaman 416:25-417:12; 425:19-25.) Dr. Westreich never opined that 1-2 ng/mL was the "therapeutic level" for naltrexone treatment.[20] Instead, Dr. Westreich agreed with Dr. Weiss that the Comer paper reported "negligible" blood plasma levels of naltrexone (***around 0.3 ng/mL***) antagonized heroin's effects. (PFOF ¶¶ 114, 155 n.15.) Teva cannot claim that a POSA would have followed Comer's teachings, but then (1) ignore Comer saying that "negligible" plasma levels antagonize the effects of heroin, and also (2) target plasma levels around ***six times higher*** than the "negligible" levels that Comer reported antagonized heroin's effects.[21] (COL ¶ 282; PFOF ¶¶ 114, 155 n.15; R-PFOF ¶¶ 130-131, 157-158, 166.)

Having failed to prove obviousness using the prior art it relied on at trial, Teva's post-trial brief turns again to Alkermes's own work as its obviousness defense, citing an email of a former Alkermes employee (Mr. Bartus) stating that he thought 1-2 ng/mL "represents the plasma therapeutic levels accepted by the opinion leaders in the field." (Teva Br. at 20 (citing TPFF ¶ 253).)[22] This internal, confidential email (and any opinion reported therein) is not published prior

[20] On cross-examination, Dr. Westreich admitted that he did not cite Verebey as supporting obviousness. (Westreich 194:14-18.)

[21] Dr. Westreich also admitted that BioTek's submission to NIDA "does not mention 2 [ng/mL] blood levels as a therapeutic target for a long-acting naltrexone product," but instead discusses "the therapeutic target for the long-acting naltrexone treatment is . . . about 150 [mg] of naltrexone a month." (Westreich 204:24-206:1 (discussing 1995 SBIR Grant at .0002).)

[22] Teva also cites TPFF ¶ 254, which is another improper attempt by Teva to pass off alleged impeachment attempts as established evidence in this case. However, the document being discussed is not even in evidence, and Dr. Ehrich ***never*** "stated in a public presentation in San Juan in 2000 that 'adequate blood levels' of naltrexone include those 'greater than 2 nanograms per milliliter for a sufficient duration, e.g., one month,'" as Teva alleges. (*See supra* Section IV.A.)

art available for a POSA and is irrelevant to an obviousness analysis. (R-COL ¶ 522.) Further, none of Teva's witnesses relied on this email at trial or showed it would provide motivation for a POSA, especially when 1-2 ng/mL was rejected by the Comer paper in 2001. (R-PFOF ¶ 182.)

4. Teva Failed to Prove a POSA Would Have Had a Reasonable Expectation of Success in Treating Dependence With a Long-Acting Naltrexone Formulation Meeting All Claim Elements as of April 2004

Rather than prove by clear and convincing evidence that a POSA would combine references to achieve the invention with a reasonable expectation of success, Teva provides only conclusory assertions and a chart with "X's" that allegedly "summarizes Dr. Westreich's and Dr. Yaman's testimony regarding where each limitation of the asserted claims can be found in Comer, Nuwayser, or Leavitt." (Teva Br. at 23-24.) But this is a far cry from what the law requires (COL ¶¶ 290, 295), *i.e.*, "a clear, evidence-supported account of the contemplated workings of the combination," *Personal Web Techs., LLC v. Apple, Inc.*, 848 F.3d 987, 994 (Fed. Cir. 2017).

Teva argues that the Comer paper teaches a successful method of treatment because the claim term "treating" has been construed by other courts to require only "that there is an attempt to care for the patient or create an improvement." (Teva Br. at 24-25; TPFF ¶¶ 354-356.) Teva's new assertion that a method of treatment claim does not require an individual to be actually treated is nonsensical, especially when considering that Dr. Westreich acknowledged that "a POSA in 2004 would have been looking for a long-acting naltrexone ***treatment*** that was safe and ***effective*** and would ***improve patient compliance*** compared to oral naltrexone." (Westreich 178:7-11 (emphases added); *see also* R-PFOF ¶¶ 234-243; R-COL ¶¶ 514-515.) It was Teva's burden to prove reasonable expectation of success of such a treatment, which Teva failed to do.

The experts agreed that the Comer paper was not treating patients afflicted by dependence, but rather subjects were ***excluded*** if they were seeking treatment and subjects were ***given heroin*** during the study. (Alkermes Br. at 13, 27; PFOF §§ IV.B, IV.C.8, VI.B.3.) Dr. Westreich admitted

that he was not offering an opinion that the Comer paper was a study to provide medical care to patients, agreeing that he offered no opinion that a "person emerging from the [Comer] study was less dependent on heroin than when they started." (Westreich 188:13-16; *see also* PFOF ¶ 189.) In fact, the Comer paper concluded that "[f]uture studies" would be needed to "evaluate the clinical utility" of the formulation for treatment because it had not been determined whether or not the BioTek formulation could be used to treat patients. (Comer at .0015; Alkermes Br. at 13-14, 27; PFOF ¶ 190, § IV.C.8.) The prior art does not, however, reflect further studies by BioTek (including with any new formulations). (*See id.*)

In particular, the evidence showed that the next BioTek publication, the Nuwayser patent, "has no information on the use of a naltrexone formulation other than the copy" of Figure 1 from the Comer paper. (Westreich 209:24-210:2; *see also* PFOF §§ IV.B, IV.C.9.) In fact, Dr. Westreich went so far as to admit that he had "not cited ***any*** prior art publication reporting use of a BioTek formulation and achieving a reduction in opioid dependence." (Westreich 204:9-12 (emphasis added); *see also* Alkermes Br. at 13-14, 27-28; PFOF ¶¶ 98-99.)

Teva also mischaracterizes the Comer paper as establishing that Depotrex "provided 'safe, effective, [and] long-lasting' ***treatment for addiction***." (Teva Br. at 6 (emphasis added); *see also id*. at 22.) The sentence of the Comer paper that Teva repeatedly cites does not discuss treatment for addiction, but rather "***antagonism of the effects of heroin***."[23] (Comer at .0007 (emphasis added).) This is referring to various criteria that were tested in the Comer paper to see the effects of naltrexone on persons ***receiving heroin***, such as pupil dilation. (PFOF ¶ 113.) Importantly, the Comer paper reported an increase in the cravings for heroin in subjects receiving 384 mg of

[23] In contrast, the clinical trials of Vivitrol® demonstrated efficacy in treating opioid dependence, measured in "opioid-free weeks." (Vivitrol® Label (2020) at .0026-27; *see also* PFOF ¶¶ 55, 132-139; Weiss 606:2-19.)

naltrexone. (PFOF ¶¶ 116-118.) The Comer study was not designed to show safety and efficacy for a treatment method, and did not claim that it had made such a finding.[24] (Alkermes Br. at 27; PFOF §§ IV.C.8, VI.B.3.)

Teva argues that in the prior art, "[t]he most successful entity was BioTek" (Teva Br. at 20),[25] but ignores that BioTek never brought forth "an injectable naltrexone product that can be prescribed to humans." (Kerrigan (5/3/22) Tr. 55:4-7, 55:20-23; PFOF ¶¶ 98-99.) Accordingly, the '499 Patent does not "deprive the public of a treatment that had been publicly disclosed years before the patent" as Teva claims. (Teva Br. at 3.) Teva certainly could use the BioTek formulation in two injections of 192 mg if Teva wished to do so, but Teva has no basis to conclude this would be a successful treatment, and Teva is not seeking FDA approval for that use. Teva instead copied Vivitrol®. (PFOF § VII.F.) Put simply, Teva has not proven by clear and convincing evidence that, as of April 2004 and without hindsight, a POSA would have had a reasonable expectation of success in achieving a treatment method with therapeutic effect, especially in light of the expressed observations in the prior art about increased cravings (PFOF §§ IV.C.8, VI.B.3) and injection site reactions (PFOF §§ IV.C.7, VI.B.3). Further, Teva failed to prove that a POSA would reasonably expect success for a treatment with a long-acting formulation

[24] Teva also crop-quotes from the Comer paper when it says that "Comer reported 'exciting' results from use of the 384-mg Depotrex formulation." (Teva Br. at 24; *see also id.* at 6.) The statement Teva cites by Comer and BioTek co-author Nuwayser expresses hope for "***a formulation*** of naltrexone," and the authors make clear in the next sentence that "[f]uture studies in our laboratory will evaluate the clinical utility of [Depotrex]." (Comer at .0015 (emphasis added); PFOF ¶¶ 117, 190.) No such future studies were reported in the prior art. (PFOF ¶ 190.)

[25] Teva boldly, but baselessly, asserts that BioTek was the "most successful entity" at the time because it "made it all the way to Phase II clinical trials" (Teva Br. at 20), but no publication supports this allegation. In fact, Teva's witnesses described the Comer paper only as a "Phase I study" (Yaman 427:3-5; *see also* Kerrigan (5/3/22) Tr. 56:10-22), and the next BioTek publication, the Nuwayser patent, "has no information on the use of a naltrexone formulation other than the copy" of Figure 1 from the Comer paper (Westreich 209:24-210:2).

that had a three-fold higher naltrexone exposure compared to the optimal dose of oral naltrexone. (Alkermes Br. at 28; PFOF ¶¶ 193-197; COL ¶ 290.)

C. Teva Failed to Prove, by Clear and Convincing Evidence, That Claims 2, 10, and 13 Would Have Been Obvious Over Comer, Nuwayser, and Leavitt

Throughout this litigation, Teva has consistently minimized the asserted dependent claims, relegating its discussion of them to a chart in its brief (Teva Br. at 23-24) and a few paragraphs for each claim in its proposed findings of fact (TPFF § V.B.2, ¶¶ 385-411). Putting "X's" purporting to "summarize Dr. Westreich's and Dr. Yaman's testimony" about where the claim limitations are found in Comer, Nuwayser, and Leavitt does not meet Teva's heavy burden of proof. (COL ¶¶ 290, 295; R-COL ¶ 539.) And, even if it could, the trial record does not support the "X's" in Teva's brief. Teva cannot evade its burden to prove ***each*** dependent claim obvious by clear and convincing evidence. 35 U.S.C. § 282; *Dana Corp. v. Am. Axle & Mfg.*, 279 F.3d 1372, 1376 (Fed. Cir. 2002) (the court erred in not separately evaluating each claim's validity). Teva did not meet this burden of proof.

1. Teva Fails in Its Effort to Use Comer as a Treatment of Alcohol Dependence to Satisfy the Requirements of Claim 10

Teva argues that "a POSA would have understood from Comer" that 384 mg of Depotrex "would be a useful treatment for alcohol dependency" (TPFF ¶ 403), but Comer expressly excluded "individuals afflicted by alcohol dependency" (Westreich 186:11-22; PFOF § IV.C.8.) Kranzler, BioTek's last publication involving alcohol dependence, tested a 206 mg naltrexone injection (far less than the amount required by Claim 10 incorporating Claim 1) (PFOF §§ IV.C.7, VI.D), which according to Teva was safe and effective for that purpose (TPFF ¶¶ 400-401; PFOF ¶ 212). Kranzler then suggested ***reducing*** the amount of naltrexone per injection for tolerability reasons. (PFOF ¶ 109.) Teva's reliance on Comer's reference to Kranzler thus cannot show that a POSA would have been motivated (without hindsight) to treat alcohol dependence by

substantially increasing the amount of naltrexone by about 50% to 384 mg naltrexone, and achieving about a three times greater AUC over oral naltrexone as Claim 10 requires.[26] (Alkermes Br. at Argument § I.E; PFOF ¶ 212; R-PFOF ¶¶ 286-296.)

2. Teva Has No Evidence of a Treatment Using Repeated Administrations for a Period of Six Months as Required by Claim 2

Teva cites the Comer paper's disclosure that "a formulation of naltrexone that requires only once-a-month administration has important and exciting treatment implications" (*see* Teva Br. at 23; TPFF ¶ 386; *see also* Comer at .0015), but this sentence indicated only the authors' desire for a once-monthly treatment method. That desire does not establish, by clear and convincing evidence, that a POSA would have had a reasonable expectation in achieving a successful treatment method after repeated injections for six months. For that question, a POSA would read the actual content of the prior art studies for what they did and did not show. *See, e.g.*, *Institut Pasteur v. Focarino*, 738 F.3d 1337, 1345-46 (Fed. Cir. 2013) ("The desire for [a certain] payoff [in the prior art] could motivate pursuit of the method, but 'knowledge of the goal does not render its achievement obvious.'"); R-PFOF ¶¶ 276-282; R-COL ¶¶ 532, 551. None of the prior art involved repeated administrations of long-acting naltrexone, let alone taught a successful treatment after repeated injections over a period of six months. (PFOF ¶ 214.)[27]

[26] Nor can Teva find help from Leavitt. (*See* Teva Br. at 24; TPFF ¶ 402.) Leavitt contains ***no information on long-acting naltrexone formulations***, and merely summarizes trials relating to ***oral*** naltrexone (50 mg per day) for treating alcohol dependence. (*See* PFOF § IV.C.10.)

[27] In contrast, the clinical trials of Vivitrol® demonstrated efficacy in treating opioid dependence, measured in "opioid-free weeks," in a ***24-week***, placebo-controlled, multi-center, double-blind, randomized trial of opioid-dependent (DSM-IV) outpatients," where ***250 subjects*** "were treated with an injection ***every 4 weeks*** of VIVITROL 380 mg or placebo." (Vivitrol® Label (2020) at .0026-27 (emphasis added); *see also* PFOF ¶¶ 55, 132-139; Weiss 606:2-19.)

Teva asserts that the Comer paper "disclosed that naltrexone can be administered over one year," again incorrectly implying the Comer paper disclosed a treatment with repeated injections every month. (*See* TPFF ¶ 387.) Contrary to Teva's assertion, Dr. Westreich agreed that "Comer did not repeat administrations over a period of time."[28] (Westreich 190:10-19; PFOF ¶ 214.) Teva is citing a place where the Comer paper was discussing treatments with 50 mg/day ***oral*** naltrexone. (Westreich 190:21-192:16.) Likewise, Teva cites Leavitt's disclosure of "longer-term therapy (6 to 9 months)" (TPFF ¶ 388), which again was only for 50 mg/day ***oral*** naltrexone (*see* PFOF § IV.C.10).

3. Teva Fails to Prove That a Formulation Containing About "35%" Naltrexone, as Required by Claim 13, Would Have Been Obvious From Nuwayser

The sole basis and "sum total" of Teva's arguments related to Claim 13 are premised on a single sentence in Nuwayser disclosing a range of "***0.1 to 80% or more*** by weight" of an "active ingredient"[29] and the assertion that "35% falls within" that range. (TPFF ¶¶ 404-411 (emphasis added).) As Dr. Little explained, however, a POSA would understand that broad range as accounting for the span of different active ingredients discussed in the patent. (*See* Little 830:23-832:4; *see also* PFOF § VI.C.) Teva ignores that, for the active ingredient ***naltrexone***, the numbers in Nuwayser were always ***more than 50%*** by weight. (PFOF ¶¶ 297-304.) The patent was consistent with the previous public grant to BioTek which, Dr. Westreich explained, was "targeted to contain ***more than 50% drug***." (1995 SBIR Grant at .0002 (emphasis added); *see* PFOF § VI.C.) The examples of a long-acting naltrexone formulation in Nuwayser thus contained ***above***

[28] Further "none of the BioTek studies, in fact, involved giving the BioTek Depotrex formulation every month to individuals for a period of 24 weeks." (Westreich 190:14-19; PFOF ¶ 214.)

[29] This disclosure in Nuwayser related to "25 specific active ingredients" and "a general description of even more possible active ingredients." (Westreich 213:11-214:15.)

50%, *e.g.*, 68.2% and 54.4% naltrexone. (*See* Westreich 214:22-215:11, 216:4-8; *see also* Nuwayser at .0018 (14:47-49), .0021 (19:22-23); PFOF § VI.C.) Teva fails to provide a non-hindsight reason for a POSA to deviate from the prior art teachings of more than 50% naltrexone to arrive at the claimed 35% naltrexone. (PFOF § VI.C.)

Teva is wrong that "[t]he burden is on Alkermes" to show the claimed 35% was "special or critical." (TPFF ¶ 410.) Teva has the burden of proving obviousness, and the cases it cites are inapposite.[30] (COL § X.D.4; R-COL ¶¶ 547-549; R-PFOF ¶¶ 303-304.) To suggest that a POSA would have been motivated to use 35% naltrexone based on a range "so broad as to encompass a very large number of possible distinct" choices is untethered to reality. *See Genetics Inst.*, 655 F.3d at 1306-7; *Merck Sharp & Dohme B.V. v. Warner Chilcott Co.*, 711 F. App'x 633, 637 (Fed. Cir. 2017).[31]

D. Teva's Attacks on the Objective Indicia Fail

Teva's assertion that Alkermes failed to prove that there is a nexus between the objective indicia and the Asserted Claims (Teva Br. at 34-35) ignores that nexus is presumed because the experts agree that the FDA-approved use of "Vivitrol is an embodiment of the '499 patent" (Yaman 397:17-19; *see also* Little 834:19-836:16; PFOF § VII.A). *See, e.g., WBIP, LLC v. Kohler*

[30] Contrary to Teva's assertion, even Teva's case law notes that, where an extremely broad range encompasses a narrow one, it does not mean that narrow range would have been obvious. *See, e.g., E.I. du Pont de Nemours & Co. v. Synvina C.V.*, 904 F.3d 996, 1006 (Fed. Cir. 2012) (citing *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1306-7 (Fed. Cir. 2011)).

[31] *See also Impax Lab'ys, Inc. v. Lannett Holdings Inc.*, 893 F.3d 1372, 1379-81 (Fed. Cir. 2018) (affirming no reasonable expectation of success where, in part, the prior art's "teachings seek to provide pharmaceutically effective formulations for active ingredients" but "offers a laundry list of potential active ingredients, including over twenty-five categories or examples of medications." (internal quotation marks omitted)); *see, e.g., In re Gordon*, 733 F.2d 900, 902 (Fed. Cir. 1984) ("The mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of the modification."); R-COL ¶ 548.

Co., 829 F.3d 1317, 1329-30 (Fed. Cir. 2016) ("[T]here is a presumption of nexus for objective considerations when the patentee shows that the asserted objective evidence is tied to a specific product and that product is the invention disclosed and claimed in the patent.") (internal quotation marks omitted). Teva's cited case, in fact, supports this presumed nexus.[32]

Teva argues that the existence of "18 other patents" covering Medisorb® means no nexus exists (Teva Br. at 34-35; TPFF § V.C.1), but the invention of the '499 Patent (embodied by Vivitrol®) is more than just Medisorb®.[33] (*See* Little 836:17-837:16.) The claimed invention here is a combination package: (1) a method of treating dependence, (2) using a single injection of a long-acting formulation containing a specified amount of naltrexone and PLGA polymer, (3) where the formulation achieves the claimed AUC levels. (*See* Little 791:25-792:17, 835:1-836:15; *see also* '499 Patent at .0017 (Claim 1).) This total package of Vivitrol® provides favorable outcomes for patients. (*See* Little 791:25-792:17, 835:1-837:16; *see also* Alkermes Br. at 33.) Moreover, Medisorb® is an inactive ingredient providing no clinical benefit to patients (PFOF § VII.A), and PLGA polymers (not just Medisorb®) ***are*** actually claimed in the '499 Patent, so the presumption of nexus remains intact.[34] (R-COL ¶¶ 564-567 (Medisorb® is not a "critical unclaimed feature."); Teva Br. at 35.)

Teva offers only unsupported conclusions to argue that the benefits of Vivitrol® are attributable to "prior art features in isolation" or "what was known in the prior art or features that

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[32] Teva's case states that a presumption of nexus exists where "the asserted evidence is tied to a specific product and that the product '*is* the invention disclosed and claimed.'" *Fox Factory, Inc. v. SRAM, LLC*, 944 F.3d 1366, 1373 (Fed. Cir. 2019) (emphasis in original).

[33] Dr. Yaman's trial testimony addressed only ***one*** of these patents at trial, and he later admitted it "does ***not*** disclose a long-acting naltrexone formulation." (Yaman 375:8-376:15, 426:9-11.)

[34] PLGA polymers (including Medisorb®) are an "inactive ingredient" (Yaman 411:13-21; Vivitrol® Label (2020) at .0036), which Teva's cited cases find does not "destroy the nexus between the claim and the product." *See, e.g.*, *Teva Pharms. Int'l GmbH v. Eli Lilly & Co.*, 8 F.4th 1349, 1361 (Fed. Cir. 2021).

are not covered by the claims." (Teva Br. at 35.) As Dr. Westreich admitted, "the benefits that Vivitrol offers to patients over oral naltrexone" are what drive the desirability of Vivitrol®. (Westreich 228:13-18.) And these benefits and favorable patient outcomes flow from the combined claimed components of the '499 Patent (PFOF ¶¶ 218-221, 233; COL § X.E.1). *See WBIP*, 829 F.3d at 1330-31 ("[T]he patent owner can show that it is the claimed combination as a whole that serves as a nexus for the objective evidence."). The mere fact that certain claim elements of the '499 Patent, individually, such as the compound naltrexone or the polymer PLGA, were known in the prior art is insufficient to prove a lack of nexus for the claimed combination of elements. *See, e.g., id.* at 1329-37 (objective indicia supported nonobviousness where one prior art reference disclosed all but two claim limitations, and those two limitations were known in the prior art).

Teva's other arguments about Alkermes's objective indicia ignore the full scope of the evidence. For example, Teva ignores reality when it asserts that "Vivitrol did not satisfy any relevant long-felt but unmet need" because "Depotrex previously succeeded in meeting the need" (Teva Br. at 37): (1) Depotrex was said by Comer to result in increased cravings in the higher dose given (as two injections) to heroin dependent subjects, and high rates of induration were reported for the 206 mg dose used in Kranzler (PFOF §§ IV.C.7-8), (2) BioTek did not advance its problematic Depotrex formulation in development[35] (PFOF ¶ 99), and (3) Depotrex was not

[35] Teva's assertion that "BioTek simply lacked the finances to continue the regulatory approval process" is unsupported by actual evidence of BioTek finances and lacks credibility. (Teva Br. at 38.) BioTek had been pursuing its formulation since the mid-1980s, running multiple studies, and by the time of the Nuwayser patent there was no clear path forward — Kranzler was saying to reduce the amount per injection from 206 mg, and Comer used two injections, with a lower amount per injection, that showed increased cravings for heroin in subjects. (PFOF §§ IV.C.7-8, VI.B.1.) Teva also ignores that another company could have sought to acquire BioTek and continue its development if its data was promising. Because there was a long-felt but unmet need for a long-

available for doctors to use in treating patients (PFOF ¶¶ 99, 301 n.41; R-PFOF ¶¶ 534-544). The evidence shows that Depotrex ***did not*** satisfy the need for a long-acting treatment. (COL § X.E.2; R-COL ¶¶ 578-579.) And the law holds that the mere existence of a prior-art publication cannot substitute for an actual functioning product in use or demonstrate satisfaction of a market need. (R-COL ¶¶ 572, 578-579.)

Teva also incorrectly asserts that "there was no related failure of others." (Teva Br. at 37.) The evidence at trial showed (and Teva's witnesses agreed) others did try and fail to make a safe and effective treatment of dependence with improved patient compliance. (*See, e.g.*, Chiang 1984; Chiang 1985; *see also* PFOF §§ IV.B, VII.C; R-PFOF ¶¶ 534-544.)

Further, in arguing no unexpected results, Teva ignores the undisputed evidence at trial: Alkermes showed in its clinical trials that the 190 mg dose of naltrexone did not show a statistically significant result in actual treatment for alcohol dependence. (PFOF § VII.E; *see* Westreich 223:16-224:2.) Teva's own witness agreed that "a provider [would] appreciate the benefits of the 380 [mg] dose compared with the 190 [mg] dose." (Westreich 223:16-224:2.) And Vivitrol® did not show higher cravings in patients during treatment. (PFOF ¶ 238.)

In arguing lack of skepticism, Teva not only applies the wrong legal standard (*see* R-COL ¶ 581), but fails to address Alkermes's evidence of industry skepticism after Vivitrol®'s launch (*see* Alkermes Br. at 34-35; PFOF § VII.D).

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acting naltrexone treatment, if Teva is correct that Depotrex was a safe and effective treatment option capable of meeting that need, given the history of searching for a long-acting treatment, it is difficult to believe that BioTek would not have pursued and received more funding if it needed it. (*See* PFOF § VII.B.)

Teva similarly ignores case law finding evidence of copying supports nonobviousness in the context of a generic drug litigation (*see* R-COL ¶¶ 582-583), and leaves wholly unrebutted Alkermes's evidence of copying (*see* Alkermes's Br. at 35-36; PFOF § VII.F).

V. Teva's "Alternative" Written Description Argument Fails on the Law and Facts at Trial

Just because Teva failed to prove that an AUC three-times higher in comparison to oral naltrexone was an inherent property of the particular BioTek formulation used in Comer (*supra* Section IV.B.1), does not mean that Teva proved instead that a POSA ***with knowledge of the '499 Patent's teachings*** would think that the inventor lacked possession of the claimed invention (Alkermes Br. at 38-40; PFOF §§ III.A, IX; COL § X.G). They are unrelated inquiries. (*Id.*)

Teva argues that "the patent provides only a single ***working*** example" (Teva Br. at 39 (emphasis added)), but that does not demonstrate a lack of written description. *See Martek Biosciences Corp. v. Nutrinova, Inc.*, 579 F.3d 1363, 1371 (Fed. Cir. 2009); *Falkner v. Inglis*, 448 F.3d 1357, 1366 (Fed. Cir. 2006) (citation omitted) ("A claim will not be invalidated [for lack of written description] simply because the embodiments of the specification do not contain examples explicitly covering the full scope of the claim language."); *see also* COL § X.G. Moreover, Teva admits that the specification "provides further description of the Medisorb polymer" beyond the working example, as well as "additional extended-release systems."[36] (Teva Br. at 39-40.) This is more than enough for adequate written description, where the specification "taught the desired characteristics" of the invention and "those of skill in this art know that those characteristics define the claimed products." *See Union Oil Co. of Cal. v. Atlantic Richfield Co.*, 208 F.3d 989, 1000-1001 (Fed. Cir. 2000). Despite Teva's legally unsupported argument that the patent specification

[36] Teva implicitly admits that Dr. Yaman was incorrect when he said that the specification "didn't give any other examples, other than [Medisorb®]." (Yaman 384:18-386:21.)

must explicitly state "how to achieve the claimed AUC results" (Teva Br. at 39-40; *see* R-COL ¶¶ 584-602), Dr. Yaman admitted that a POSA would have known how to make long-acting formulations according to the '499 Patent to achieve the claimed AUC. (PFOF ¶¶ 267-270; R-PFOF ¶¶ 464, 467-468, 472, 476.)

Teva's arguments are also based on the incorrect assertion that the specification "does not provide any information as to the ratio of lactic acid to glycolic acid of the PLGA polymer" (TPFF ¶¶ 586-587), but the specification exemplifies the PLGA ratio of 75:25 and describes how changing the ratio impacts the formulation (PFOF ¶¶ 269-270). Dr. Yaman never showed that a POSA with this wealth of information from the specification and their own prior knowledge, including knowledge of how changing the ratio would affect blood plasma levels, would have been left believing the inventor lacked possession of the claimed invention. (PFOF ¶¶ 268; R-PFOF 461-477.)

VI. Conclusion and Remedy

For the reasons set forth above, as well as in Plaintiffs' opening post-trial submissions and their responsive Proposed Findings of Fact and Conclusions of Law, Plaintiffs respectfully request that the Court find that Teva has failed to meet its burden of proving, by clear and convincing evidence, that the Asserted Claims are invalid. As such, Plaintiffs are entitled to an Order pursuant to 35 U.S.C. § 271(e)(4)(A) that the effective date of any approval of Teva's ANDA No. 213195 be a date that is not earlier than the expiration of the '499 Patent.

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Respectfully submitted,

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